



APPELLANT'S BRIEF

In re application of Walt et al.:
Self-Encoding Fiber Optic Sensor

Serial No. 08/944,850

Filed: October 6, 1997

Examiner: C. Hannaher

Group Art Unit: 2878

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PATENT

Attorney Docket No.: A-67207/RMS/DCF [469420-56]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:) Examiner: HANNAHER, C.
WALT *et al.*)
Serial No.: 08/944,850)
Filed: October 6, 1997)
For: SELF ENCODING)
FIBER OPTIC SENSOR)

)

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APPELLANT'S BRIEF

Honorable Commissioner for Patents
Washington, DC 20231

Sir:

This appeal brief, filed in triplicate in connection with the above-captioned patent application, and is in response to the final Office Action mailed June 20, 2002. This appeal is taken pursuant to Rule 1.192, following the Notice of Appeal filed September 18, 2002, along with the requisite fee set forth in 37 CFR § 1.17(c). It is also accompanied by a petition for a five month extension of time and the requisite fee set forth in 37 CFR § 1.17(a).

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Appellants also request an oral hearing under 37 CFR §1.194 and encloses the required fee pursuant to 37 CFR §1.17(d).

The Commissioner is authorized to charge any fees, including extension fees or any other relief as may be required or credit any overpayment to Deposit Account No. 50-2319 (Our Order No. A-67207/RMS/DCF [469420-56]).

I. REAL PARTY IN INTEREST

The real party in interest is The Trustee of Tufts College, Medford, Massachusetts, the owner by assignment of the above-identified patent application. Furthermore, Illumina Inc. is the exclusive licensee of this application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences which will directly affect, be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

The present application was originally filed with Claims 1-27. In response to a Restriction Requirement, Claims 18-23 were cancelled without prejudice or disclaimer. New Claims 28-38 were added. In an Office Action dated August 11, 1999, Claims 1-17 and 24-27 were withdrawn from consideration. In response to the Office Action, Claims 1-17 and 24-27 were cancelled without prejudice or disclaimer as drawn to a non-elected invention. Claims 28

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and 37 were amended. In a subsequent Response to Office Action mailed September 14, 2000, Claim 32 was further amended. During an Examiner's Interview on November 2, 2000, a second Preliminary Amendment was filed canceling Claims 28-38 and submitting Claims 39-48. Subsequently, the Examiner issued an Office Action based on Claims 28-38 which had been previously cancelled. In a Communication mailed February 13, 2001, Appellants requested a new Office Action that is directed to the pending claims, Claims 39-48. This request was granted, and in an Office Action mailed August 28, 2001, Appellants amended Claims 39-41, 43, 44 and 46. The claims on Appeal, Claims 39-48, as currently pending are set forth in Appendix A.

IV. STATUS OF AMENDMENTS

No amendments to the claims have been made subsequent to the final rejection of those claims herein.

V. SUMMARY OF INVENTION

The general invention is directed to sensor arrays, particularly biosensor arrays, and methods of using and processing the signals that are generated from the sensor arrays upon exposure to a target analyte.

The general apparatus of the invention includes arrays comprising a plurality of different sensor elements, each of which is present as its own plurality. That is, the total population of different sensor elements that comprise the array is divided up into subpopulations of individual sensor elements, such that there are multiple copies of each sensor element on the array. For ease of understanding, this is exemplified in a non-limiting way by a preferred embodiment, wherein the sensor elements are microspheres, or beads, distributed on a surface. Thus the total

population of beads is made up of subpopulations of beads, with each subpopulation carrying a different capture probe (e.g. a nucleic acid probe). The bead subpopulations are generally individually made, and then mixed together to form a pool, which is then distributed on the surface. Thus multiple beads of each subpopulation go down on the surface. Accordingly, there is a sensor redundancy built into the array.

In general, sample containing target analytes are added to the sensor arrays of the invention, fluorescent signals are measured for each sensor element, and the signals from sensor elements of the same subpopulation are added together (summed).

The distinct advantage of such a system (claimed specifically in claim 47) is that due to this redundancy, the signal-to-noise ratio of the array can be increased by this "sensor element signal summing". That is, by measuring the signal associated with each sensor element of the multiplicity of sensor elements in the subpopulation and then adding them together, better results are obtained.

Accordingly, the invention provides for an assay method comprising providing a sensor array comprising a first subpopulation comprising first sensor elements and a second subpopulation comprising second sensor elements. The method further comprises adding a sample comprising a first target analyte that binds to the first sensor elements and measuring a first fluorescent signal of a first of said first sensor elements and a second fluorescent signal of a second of said first sensor elements and summing the first and second fluorescent signals (Claim 39).

Support for the claims is found throughout the specification and claims as filed. In particular claim 39 finds support in claims 21 and 26 as filed. In addition, claim 39 finds support at p. 13, line 7. Claim 40 finds support throughout the specification as filed, for example at p. 9,

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line 14, and p. 12, lines 14-20. Support for claim 41 is found throughout the application and claims as filed. Support for claim 42 is found throughout the application, for example at p. 12, line 5. Support for claim 43 is found at p. 24, line 6. Support for claims 44 and 45 is found in Table IV. Support for claim 46 is found in claim 18 as filed. Support for claim 47 is found in claims 18 and 19 as filed and throughout the specification as filed. Support for claim 48 is found throughout the specification and claims, for example claim 24, as filed.

VI. ISSUES

The final Office Action mailed September 20, 2002, presents three issues for which Appellants request review:

- 1). An issue of patentability under 35 U.S.C. § 102(e) of Claims 39, 40, 43-45, 47 and 48 as anticipated by Pinkel et al. (U.S. Patent No. 5,690,894A, ('894)(Exhibit A));
- 2). An issue of patentability under 35 U.S.C. § 103 of Claim 46 as being obvious over Pinkel et al. (U.S. Patent No. 5,690,894A('894));
- 3). An issue of patentability under 35 U.S.C. § 103 of Claim 41 and 42 as being obvious over Pinkel et al. (U.S. Patent No. 5,690,894A('894)) in view of Lough et al. (U.S. Patent No. 5,900,481A ('481)(Exhibit B)).

VII. GROUPING OF CLAIMS

For purposes of appeal, Claims 39, 40, 44-45 and 48 are grouped together as the first group and stand or fall together, independently from the other groups.

Claims 41 and 42 are grouped together as the second group and stand or fall together, independently from the other groups.

Claim 46 comprises the third group and stands independently from the other groups.

Claim 47 comprises the fourth group and stands independently from the other groups.

The groups are considered separately patentable for the reasons presented below.

VIII. ARGUMENT

REJECTION UNDER 35 U.S.C. § 102(e) SHOULD BE WITHDRAWN

1. ARGUMENT IN SUMMARY

The rejection of claims 39, 40, 43-45, 47 and 48 is based on the Examiner's assertion that the '894 patent teaches an assay method corresponding to use of the apparatus disclosed in Figure 4 of the '894 patent. The Examiner states that the assay method disclosed in the '894 patent comprises:

- a) measuring first fluorescent signals of at least two of the sensor elements of the first subpopulation with detectors and
- b) summing the first fluorescent signals.

Thus, the Examiner's position is that the '894 patent thus anticipates the rejected claims.

The Appellants submit, in contrast, that the '894 patent does not disclose measuring and summing individual signals from individual sensor elements of a subpopulation of sensor elements. Rather, the Appellants submit that the Examiner has confused the definition of a "sensor element" of the present invention with the prior art elements of multiple optical fibers that make up a single array element.

2. DETAILED ARGUMENTS

The rejection of claims 39, 40, 43-45, 47 and 48 as being anticipated by Pinkel ('894) is in error and should be withdrawn.

The rejection of claims 39, 40, 43-45, 47 and 48 is based on the Examiner's assertion that the '894 patent teaches a method that corresponds to the use of the apparatus disclosed in figure 4.

Summary of the '894 Patent

The '894 patent is generally directed to the use of biosensors comprising an array of optical fibers where each fiber has an attached "biological binding partner". (See abstract). In some cases, the array has single fibers for each biological binding partner. In other cases, a group of fibers, each bearing the same biological binding partner, is used. (See column 9, lines 10-25).

The '894 patent describes three different detector configurations. In the first case, the detector is arranged to read the aggregate signal, as a single signal, from the entire transmission face of the biosensor (see column 9, lines 12-14). Alternatively, the detector is arranged to read the signal from single optical fibers. (See column 9, lines 22-23). Finally, the detector may be arranged to read the signal from a group of optical fibers all bearing the same species of biological binding partner. Again, this is done as a single signal. In no situation does the '894 patent describe taking two readings and summing them together.

Arguments

The Examiner asserts that the apparatus "comprises a sensor array 14 having at least two subpopulations (the groups of strands 10) of different sensor elements (sensor ends 11, where each group may have a different sensor, column 8, lines 50-67)." Accordingly, "[t]he assay method would comprise the steps of providing the sensor array 14, adding a sample 30 comprising a first target analyte that binds to the first sensor elements (e.g., first collection 25), measuring a first fluorescence signal of a first of the first sensor elements 11 and a second fluorescent signal of a second of the first sensor elements 11 (column 13, lines 33-39) with detector 20, and summing the first fluorescence signals (column 9, lines 12-14 and 21-25)." (see p. 3 of the final Office Action mailed September 20, 2002) . Appellants traverse this rejection.

As stated by the Federal Circuit in *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, **every element** of the claimed invention must be identically shown in a single reference." (Emphasis added).

Here, Appellants submit, each and every element of the rejected claims is not identically shown in the '894 patent.

Claim 39 is directed to a method comprising providing a sensor array comprising a first subpopulation comprising first sensor element, and a second subpopulation comprising second sensor elements, adding a sample comprising a first target analyte that binds to said first sensor elements, measuring a first fluorescent signal of a first of said first sensor elements and a second fluorescent signal of a second of said first sensor elements and summing said first and second fluorescent signals.

In contrast, the '894 patent teaches a method that includes providing an array of optical fibers with different biological binding partners contacting the array with a sample and measuring the signal from the optical fibers. However, there is simply no teaching in the '894

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patent of summing the measured signal from a first element of a first population of sensor elements and a second element of the first population of sensor elements.

The Examiner points to column 9, lines 12-14 and 21-25 of the '894 patent as providing the disclosure of "summing the first fluorescence signals" (see p.3, paragraph 4 of the final Office Action of September 20, 2002). However, Appellants fail to find any disclosure here that describes summing the measured signal from first and second elements of a first population of sensor elements. That is, col. 9, lines 12-14 describe that

[a] single photomultiplier or CCD element may be arranged to measure the aggregate signal provided by the entire transmission face **15** of the biosensor.

Appellants respectfully submit that this does not disclose obtaining a measurement of each individual sensor element and then summing the individual measurements. Rather, this disclosure describes obtaining a single measure of the aggregate signal from the array. That is, the claims set forth two discrete steps: 1) measuring the signal from a first and second of a first subpopulation of sensor elements; and 2) summing the signal from said first and second of a first subpopulation of sensor elements. In contrast, the '894 patent describes only measuring the aggregate signal from the array. While aggregate signal may be the sum of all signals from the array, the '894 patent does not teach measuring the signal from individual sensor elements and summing the measured signal. Rather, only the aggregate signal is measured.

In addition, the Examiner points to column 9, lines 21-25 as disclosing summing. However, Appellants submit that this disclosure fails to teach the elements of summing first and second signals from a first population of sensor elements. What is disclosed at column 9, lines 21-25 is that "the detector is preferably arranged to read the signal from single optical fibers **10** or from groups of optical fibers where all of the optical fibers **10** in a group bear the same

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species of biological binding partners." However, there is no teaching of summing the signals from the optical fibers in a group.

With specific respect to claims 41 and 42, the '894 patent does not disclose or suggest the use of beads as sensor elements, nor of these beads distributed in wells.

With specific reference to claim 46, the '894 patent does not disclose or suggest the step of adjusting the baseline of the signals prior to summing.

With specific reference to claim 47, the '894 patent does not teach the increase of the signal-to-noise ratio as a result of summing. The sole references to changes in signal-to-noise ratios have to do with the use of expanded surface area optical fibers (see column 7, line 66 to column 8, line 3), the positioning of the excitation illumination (see column 14, lines 38-44) or the use of filters in the detector (see column 21, lines 5-8).

Because not each and every element of the claims is described identically in the '894 patent, Appellants respectfully request that that the rejection be withdrawn.

**REJECTION UNDER 35 U.S.C. §103 OVER PINKEL ('894) SHOULD BE
WITHDRAWN**

1. ARGUMENT IN SUMMARY

The rejection of claim 46 as being obvious over the '894 patent is based on the Examiner's position that it would have been obvious for one of ordinary skill in the art to adjust the baseline of fluorescence signals in the method disclosed in the '894 patent because such an adjustment is a known and useful step in accurately measuring responses.

However, Appellants respectfully submit that the Examiner failed to demonstrate why one of skill in the art would have been motivated to modify the teachings of the '894 patent to

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reach the claimed invention. Moreover, Appellants submit that not all claim elements are taught in the '894 patent. As such, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

2. DETAILED ARGUMENTS

The rejection of claim 46 as being obvious over the '894 patent is in error and should be withdrawn.

Summary of the '894 Patent

As noted above, the '894 patent is generally directed to the use of biosensors comprising an array of optical fibers where each fiber has an attached "biological binding partner". (See abstract). In some cases, the array has single fibers for each biological binding partner. In other cases, a group of fibers, each bearing the same biological binding partner, is used. (See column 9, lines 10-25).

The '894 patent describes three different detector configurations. In the first case, the detector is arranged to read the aggregate signal, as a single signal, from the entire transmission face of the biosensor (see column 9, lines 12-14). Alternatively, the detector is arranged to read the signal from single optical fibers. (See column 9, lines 22-23). Finally, the detector may be arranged to read the signal from a group of optical fibers all bearing the same species of biological binding partner. Again, this is done as a single signal. In no situation does the '894 patent describe taking two readings and summing them together.

Arguments

The rejection of claim 46 as being obvious over the '894 patent is based on the Examiner's position that it would have been obvious for one of ordinary skill in the art to adjust

the baseline of fluorescence signals in the method disclosed in the '894 patent because the detector system may be employed with a computerized data acquisition system and analytical program and that such an adjustment is a known and useful step in accurately measuring responses. Appellants traverse this rejection.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Here, Appellants submit that the Examiner has failed to point to anything in the prior art that would have motivated one of skill in the art to modify the teaching of the '894 patent to reach the invention as described in claim 46. While the Examiner suggests that the skilled artisan would have been motivated to modify the teachings of the '894 patent because such baseline adjustment is a known and useful step in accurately measuring responses, the Examiner has provided no evidence of this motivation. The Examiner has pointed to no teaching in the '894 patent itself to support this. In contrast, it appears that the Examiner is relying on what is presumed to be common sense or skill in the art.

However, with regard to the former, Appellants submit that this is an inappropriate determination of motivation. That is, as noted in *In re Lee*, the Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense"". *In re Lee*, 61 USPQ2d 1430 (CA FC

2002). The Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to be derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing *In re Zurko*, 59 USPQ2d 1693 (CA FC 2001); see *Lee*, 1434-1435).

With respect to the Examiner relying on the skill in the art to perform baseline adjustment, the Appellants submit that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. See *Al-Site Corp. v. VSI International, Inc.* 50 USPQ 2d 1161 (Fed. Cir. 1999). In *Al-Site*, the patents were drawn to devices that allow consumers to try on eyeglasses and return them to the rack without removing them from their display hangers (see *Al-Site*, 1163). The defendant provided prior art that lacked certain features of the invention, but argued that it would have been obvious to punch a hole in the prior art eyeglass security tag to hang it from a support. The defendant provided no specific teaching or suggestion for making the combination, instead relying on knowledge of one of skill in the art to supply the missing suggestion to combine. The Federal Circuit stated that "[s]kill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case . . ." and upheld the validity of the patents on the obviousness issue (see *Al-Site* at 1171).

Similarly, the facts in *In re Kotzab*, 55 USPQ 2d 1313 (Fed. Cir. 2000) are applicable as well. In *Kotzab*, the claims were drawn to a method using a single temperature sensor to control a plurality of flow control valves. The primary reference disclosed multiple sensors each controlling a associated flow control valves. The Federal Circuit stated that while the idea of a single sensor controlling multiple valves, rather than multiple sensors controlling multiple valves, was a "technologically simple concept", there was an absence of motivation.

Both of these cases support Appellants' position that baseline adjustment of fluorescent signals from sensor elements is not obvious in light of the teachings of the '894 patent.

In the present case Appellants submit that the Examiner has failed to point to anything specific in the cited reference that would suggest or provide the motivation to modify the disclosure of the '894 patent to include baseline adjustment. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under *In re Lee*, *In re Kotzab* and *Al-Site*.

Moreover, Appellants again submit that the '894 reference fails to teach or suggest summing. As noted above, Appellants submit that while the '894 patent described arrays and measuring responses from sensors, there is no teaching of measuring a first response from a first sensor of a population of sensors, measuring a second response from a second sensor of the population of sensors and summing the first and second responses. As such, Appellants submit that not all claims elements are provided in the cited reference, and thus a required element of a *prima facie* case has not been met.

In conclusion, the Examiner has failed to provide any motivation for modifying the teachings of the '894 patent. Moreover, even assuming, arguendo, if there were motivation, not all claim elements are taught in the cited reference. As such, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Appellants respectfully request that the rejection be withdrawn.

**REJECTION UNDER 35 U.S.C. §103 OVER PINKEL ('894) IN VIEW OF
LOUGH ('481) SHOULD BE WITHDRAWN**

1. ARGUMENT IN SUMMARY

Claims 41 and 42 are rejected as being obvious over Pinkel et al ('894) in view of Lough et al ('481). The rejection of claims 41 and 42 as being is based on the Examiner's position that although the sensor of Pinkel does not comprise beads, Lough shows that beads are known as elements in a sensor array. With respect to claim 41, the Examiner asserts that it would have been obvious for one of skill in the art to "modify the method of Pinkel *et al.* to specify that the sensor ends 11 therein were bound to beads as suggested by Lough *et al.* (as the fiber strands 10 in Pinkel *et al.* qualify as a support as described by Lough *et al.* at column 3, line 29)."

Appellants respectfully traverse.

Summary of the '481 patent

Lough ('481) is generally directed the use of beads as supports for the attachment of nucleic acids. The beads are conjugated to a support and are further conjugated to nucleic acids. The beads can carry a variety of different functional groups for attachment.

Summary of the '894 patent

As noted above, the '894 patent is generally directed to the use of biosensors comprising an array of optical fibers where each fiber has an attached "biological binding partner". (See abstract). In some cases, the array has single fibers for each biological binding partner. In other cases, a group of fibers, each bearing the same biological binding partner, is used. (See column 9, lines 10-25).

The '894 patent describes three different detector configurations. In the first case, the detector is arranged to read the aggregate signal, as a single signal, from the entire transmission

face of the biosensor (see column 9, lines 12-14). Alternatively, the detector is arranged to read the signal from single optical fibers. (See column 9, lines 22-23). Finally, the detector may be arranged to read the signal from a group of optical fibers all bearing the same species of biological binding partner. Again, this is done as a single signal. In no situation does the '894 patent describe taking two readings and summing them together.

Arguments

As noted previously, to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Here, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has failed to point to any specific teaching in the prior art that would have motivated one of skill in the art to combine the references to reach the claimed invention. In addition, Appellants submit that not all claims elements are taught in the cited references either individually or when combined.

With respect to the lack of motivation, Appellants again note that in establishing motivation for the combination of references, the Examiner must point to specific teachings found in the prior art in order to demonstrate the teaching that would have motivated one of skill in the art to combine the references. In the present case, the Examiner has noted no specific

teaching. In fact, the Examiner mentions nothing about what would have motivated the skilled artisan to combine the references.

With respect to claim 41, the Appellants point out that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination. *In re Mills* 16 USPQ 2d 1430 (Fed Cir. 1990). Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so". Id at 1432. Here, the Examiner's silence with respect to motivation confirms a lack of a *prima facie* case.

Regarding claim 42, Appellants note that the Examiner suggests that "[t]he connection of the beads suggested by Lough *et al.* and the sensor ends 11 in the sensor array 14 provided in the method suggested by Pinkel *et al.* is a choice within the ordinary skill in the art at the time the invention was made" (see p. 5 of the Office Action of September 20, 2002). However, Appellants submit that obvious to try is not the standard in determining motivation. Simply because something is a choice within the art is insufficient to provide motivation for the combination of references. That is, Appellants submit that the Examiner is basing the rejection on the idea that the cited references render the present invention "obvious to try". Case law is clear, however, that the "obvious to try" criterion is not sufficient to support a rejection under 35 U.S.C. § 103. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). See also *The Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990).

Similarly, as argued above, the Examiner's statement that the Lough beads "were a choice within the ordinary skill of the art" does not provide the required motivation under *In re Mills*. Additionally, it is well established that a statement that modification of the prior art to meet the claimed invention would have been "well within the ordinary skill in the art at the time the

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claimed invention was made" is insufficient to establish a *prima facie* case. *Ex parte Levingood*, 28 USPQ 2d 1300 (BPAI 1993).

In addition, Appellants submit that not all claim elements are taught in the references either individually or when combined. As noted above, while '894 patent described arrays and measuring responses from sensors, there is no teaching of measuring a first response from a first sensor of a population of sensors, measuring a second response from a second sensor of the population of sensors and summing the first and second responses. Moreover, Appellants submit that the '481 patent fails to teach measuring a first response from a first sensor of a population of sensors, measuring a second response from a second sensor of the population of sensors and summing the first and second responses. As such, Appellants submit that not all claims elements are provided in the cited references.

In conclusion, the Examiner has failed to provide any motivation for combining the teachings of the '894 patent and the teaching of the '481 patent. Moreover, even assuming, arguendo, that there was motivation, not all claim elements are taught in the cited reference. As such, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Appellants respectfully request that the rejection be withdrawn.

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CONCLUSION

In conclusion, in light of the above, Appellants believe that the above arguments warrant reconsideration and withdrawal of the outstanding final rejections herein.

Respectfully submitted,

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